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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/763,276	01/26/2004	Masabumi Shibuya	249-323	6571

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EXAMINER	
NICKOL, GARY B	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 12/30/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/763,276	SHIBUYA ET AL.	
	Examiner	Art Unit	
	Gary B. Nickol Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,10-13 and 42* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,10-13 and 42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Re: Shibuya *et al.*

Claims 1-2, 10-13, and 42 are pending.

DETAILED ACTION

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 10 are rejected under 35 U.S.C. 102(b) as being anticipated by Kassis *et al.* (Clinical Cancer Res., August 1999, Vol. 5, pages 2251-2260).

The claims are drawn to a method for inhibiting KDR/Flk-1 signal transduction comprising using a substance which inhibits binding of a signal transduction molecule to 1175-tyrosine phosphorylated KDR/Flk-1 wherein the signal transduction molecule is phospholipase C-gamma.

Kassis *et al.* teach (page 2245-2255; & Figure 4) a method of inhibiting cell invasiveness comprising using a non-cytotoxic substance (U73122) that specifically inhibits the activity of phospholipase-C gamma. Further, as evidenced by Takahashi *et al.* (Oncogene, Vol. 14, 1997, pages 2079-2089) phospholipase-C gamma is on of the major substrates for KDR/Flk-1 (page 2086). Thus, in the absence of evidence to the contrary, the administration of U73122 to said

cells inherently inhibits the ability of phospholipase-C gamma to bind 1175-tyrosine phosphorylated KDR/Flk-1. *In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed method is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).*

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 2, 10-13, and 42 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 1, 10 are also rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for inhibiting KDR/Flk-1 signal transduction in-vitro with U73122, does not reasonably provide enablement for inhibiting KDR/Flk-1 signal transduction in-vivo with any and all substances, including antibodies. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in *In re* Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). There

are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to:

the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention based on the content of the disclosure. See also *Ex parte* Forman, 230 USPQ 546 (BPAI 1986).

The claims are broadly drawn to a method of inhibiting "cell growth" or signal transduction comprising using a substance that inhibits binding of a signal transduction molecule to 1175-tyrosine phosphorylated KDR/Flk-1, wherein the signal transduction molecule is phospholipase-C gamma, and wherein the substance includes an antibody which specifically recognizes 1175-tyrosine phosphorylated KDR/Flk-1 and inhibits phosphorylation of phospholipase-C gamma.

The specification teaches [para 161] that the anti-KDR antibody specific for 1175-tyrosine phosphorylation can be used for the inhibition of growth of endothelium via KDR/Flk-1. Thus, when signal transduction of the human VEGF receptor KDR can be inhibited, it is useful in diagnosing or treating diseases whose morbid states progress by abnormal angiogenesis, such as solid tumor growth, metastasis formation, arthritis in rheumatoid arthritis, diabetic retinopathy, retinopathy of prematurity, psoriasis and the like in human. The specification further teaches [para 155] that endothelial cell growth can be quantified by the addition of bromodeoxyuridine (BrdU). When the number of stained cells in the case of the injection of the

antibody is reduced in comparison with the case of no injection, it can be said that the antibody is inhibiting synthesis of DNA, namely signal of cell growth, in vivo.

Thus, claims 1 and 2 can broadly be interpreted as a method of inhibiting the growth of tumor cells in vivo comprising administering an antibody that specifically binds to 1175-tyrosine phosphorylated KDR/Flk-1.

However, the specification provides insufficient guidance and objective evidence to predictably enable one of skill in the art to use the invention as claimed. There is no evidence of reduced tumor cell growth with *any* substance that inhibits binding of a signal transduction molecule to 1175-tyrosine phosphorylated KDR/Flk-1. Further, there is no evidence that antibodies specific to 1175-tyrosine phosphorylated KDR/Flk-1 predictably inhibit cell growth either in-vitro or in-vivo. Also, there is no predictable guidance with regards to the amount of antibodies to be administered or their route of delivery. Based on mere binding studies, the specification essentially draws the conclusion that all substances that *might* disrupt the interaction between 1175-tyrosine phosphorylated KDR/Flk-1 and PLC-γ would effectively treat cancer.

However, the level of predictability in the art of treating tumors is highly unpredictable. This can be due to a number of factors. For example, Jain (Scientific American July 1994), discloses barriers to the delivery of drugs into solid tumors. These impediments include (1) Non-uniform blood delivery to all areas of the tumor in which some areas of the tumor receive therapeutic agents and other areas of the tumor receive no therapeutic agent at all. (Page 60 col. 3); (2) Increased viscosity of blood in the tumor itself which also hinders drug delivery to the tumor (see paragraph bridging pages 60 and 61); (3) High liquid pressures in the interstitial

matrix can retard the delivery of large therapeutic agents, such as antibodies, into tumors (page 61, Col. 1 paragraph 1). Further, with regard to larger molecules such as antibodies, Jain teaches that convection is a necessary mechanism by which larger therapeutics reach target cells which are not directly fed by the vasculature. However, convection is not observed in large tumors (defined as more than ½ centimeter in diameter, page 62 col. 1), and convection is necessary for adequate drug delivery of molecules having a molecular weight of more than 5000 (page 61, col. 1 through page 63, col. 3). Hence, molecules as large as antibodies (i.e., MW=150,000) would require several months to reach a uniform concentration in a tumor that measures 1 centimeter in radius (page 63, col. 2). Further, Weiner (Seminars Oncology, Vol. 26, No.4, 1999, pages 41-50) provided an overview of monoclonal antibody of therapy including some promising activity, however major obstacles to clinical efficacy still exist extending the unpredictability of this treatment. This includes impaired distribution and delivery of antibody to the tumor site, inadequate trafficking of potential cellular effectors to tumor, antigenic heterogeneity, shed or internalized targets, insufficient target specificity, and induction of HAMA (page 43). Further, the disclosure provides no objective evidence or working examples to lend one of ordinary skill in the art a reasonable expectation of success. Lack of working examples is given added weight in cases involving an unpredictable and undeveloped art such as the treatment of cancer with antibodies. In the instant case, the claims are so broadly drawn, the guidance is so limited, and the art is so unpredictable that it would require undue experimentation to successfully practice the invention as claimed.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gary B. Nickol Ph.D. whose telephone number is 571-272-0835. The examiner can normally be reached on M-Th, 8:30-5:30; alternate Fri., 8:30-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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GBN

GARY B. NICKOL, PH.D.
PRIMARY EXAMINER